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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,859	09/02/1999	JAMES SAMSOONDAR	5352-051	4860

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,859	SAMSOONDAR ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-12,23,27,34 and 38-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-12,23,27,34 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8, 10-12, 23, 27, 34 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There are two parts to this issue, the first is that the claims as now presented do not require the two measurements to be taken on different instruments since analyzers use spectrophotometers (see the next rejection). The second part to this issue is that applicant is arguing the claims require the two measurements be carried out on different instruments. As basis for this applicant has cited original claim 8 and pages 14-15 of the original specification. Examiner agrees that there is basis for using the term spectrophotometer. However, the basis for the spectrometer and the analyzer being different is not found in or supported by the paragraph bridging pages 14-15 of the instant specification as alleged. This paragraph is discussing the calibration step of the spectrophotometer and mentions the Abbott Cell Dyn ™ only in the context of determining the hemoglobin concentration in a lysate that was used to create the samples that were used in the calibration step of the spectrophotometer. This does not constitute different apparatus for measuring the sample without a reagent and in the presence of a color forming reagent. Thus there is not support in the specification as originally filed for the two measurements being carried out on different instruments. Because of this, the claims will be treated as the two measurements can be made with the same spectrometer or analyzer.

3. Claims 8, 10-12, 23, 27, 34 and 38-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 8 and 38, it is not clear if the spectrophotometer and analyzer are the same or different. In support of this applicant is directed to the applied Sagusa reference. In the paragraph bridging columns 2-3 the first two sentences teach that in the prior rate analyzers (analyzing apparatus) described the quantity of light of a

specified wavelength transmitted through the individual sample is measured by a spectrophotometer twice at different time points. From this it is clear that an analyzer can have a spectrophotometer as the detecting or measuring device.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 8, 10-12, 23, 27, 34 and 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeGrella, Corns or Waymack in view of Davis, Sagusa, Simon and Christenson, Leissing or Mullins.

In the paper DeGrella discusses a nephelometry system for the Abbott TDx analyzer. A self-contained light-scattering accessory carousel was developed for the Abbott TDx fluorescence polarization analyzer, extending the instrument's capabilities to nephelometric methods of analysis, including assays for specific proteins by immunoprecipitation: IgG, IgA, IgM, and transferrin. The scattered light from a green-light-emitting diode (peak wavelength 565 nm) is measured at an angle of 37.5° by the existing optical detection system of the TDx analyzer without modification of the instrument. Measurements are made at quasi-equilibrium, with sample blank correction. No sample pretreatment is required, and antigen-excess is checked automatically. Coefficients of variation range from 3 to 6% (within-run) and 7 to 9% (total). Calibration curves may be stored for at least 2 weeks. A nephelometric method for monitoring chromogenic reactions in the green wavelength region is also described. This method, Scattered Energy Attenuation, was used in preliminary experiments to measure Ca, total

protein, Fe, and bilirubin. Under the "Nephelometry of serum proteins" subheading (page 1475) the sample blank (initial measurement) is made during the first carousel revolution when only samples and dilution buffer are present (in the absence of a reaction step that generates a chromophore in the specimen). The second carousel revolution adds the antiserum reagent (the reagent for causing a chromophore) and takes a second measurement to determine the amount of change. Page 1476 teaches a similar procedure for chromogenic reactions. DeGrella does not teach interference by blood substitutes or calculating a correction (calibration) equation.

In the paper Corns teaches a new colorimetric method for the measurement of serum calcium using a zinc-zincon indicator. Calcium in the sample displaces zinc from an EGTA complex, the zinc then forming a blue-colored complex with a zincon indicator. The method is rapid, sensitive, and linear; it may be applied directly to serum and is readily automated. No compound tested gave rise to any interference at physiological concentration, although excessive hemolysis leads to low results being obtained. To avoid interference from endogenous zinc, a serum blank is required for each sample; this also avoids errors introduced by turbidity of the sample. The results obtained correlate well with atomic absorption spectroscopy. Page 592 teaches two methods of which the single tube method, method 2, is particularly relevant. In this method, a first absorbance reading is taken with only the sample and buffered zincon present in the tube (serum blank, figure 1a). then the reagent causing a color change is added and a second reading is taken (see figure 1b). Pages 594-595 discuss the interferences and how the serum blank corrects the problem. Corns does not teach interference by blood substitutes or calculating a correction (calibration) equation.

In the paper Waymack discusses assay instrument-dependent matrix effects in standardization of cholesterol measurements. Human serum-based frozen reference materials have been used by the Centers for Disease Control and Prevention (CDC)-National Heart, Lung and Blood Institute Lipid Standardization Program to improve the precision and accuracy of blood cholesterol measurements. Occasionally, laboratories in the program have had problems obtaining results for patients' fresh serum samples equivalent to those obtained with frozen CDC standardization pools. This incompatibility of sample, reagent, instrument, and assay characteristics has been labeled broadly as a matrix effect, which usually is attributed to unknown characteristics of the processed pool material. In this study, the authors showed that a

large negative bias obtained with CDC pools was attributable to use of the sample blank mode on the Cobas-Bio analyzer. However, under the same conditions, fresh patients' serum samples were analyzed accurately. The use of a blank absorbance immediately after mixing sample and reagents (the "autoblank" mode) allowed the instrument to accurately analyze both fresh serum samples and CDC standardization pools and thus allowed the documentation of traceability of the cholesterol measurements to the National Reference System for Cholesterol. Page 2059 discusses the two types of analysis modes used along with the equation for measuring the concentration. In the type 1 analysis the serum blank measurement occurs on diluted serum. in type 5 analysis the serum blank measurement occurs after addition of the reagent to the sample but prior to significant reaction has taken place. This value is then used to correct (subtract out) the effect of the sample or sample and reagent in the final measurement. Waymack does not teach interference by blood substitutes or calculating a correction (calibration) equation.

In the patent Davis teaches a method of detecting hemolysis in a whole-blood sample, a method of determining an elevation in the potassium ion concentration of a whole-blood sample, an apparatus for detecting hemolysis and/or determining an elevation in the potassium ion concentration in a fluid sample, an apparatus for detecting hemolysis and/or determining an elevation in the potassium ion concentration in a whole-blood sample, and a single-use cartridge containing a plurality of microfabricated biosensors which further contains a hemolysis detection unit. Thus Davis separately detects the presence of hemoglobin in the blood sample consistent with the prior art as taught in column2, lines 46-52. Columns 2-3 of the application teach the interference from hemoglobin caused through hemolysis of red blood cells through both an increase in the concentration of other components found in the red blood cells or through colorimetric interference with chromogenic reagents. In particular the above noted column 2, lines 46-52 teaches the prior method of checking the color of the plasma sample for the red coloration associated with the presence of hemolysis. Column 3, lines 12-18 list several analytes which can be affected through the presence of hemolysis including potassium, lactate dehydrogenase, cholesterol, prostatic phosphatase, aspartate aminotransferase, and alanine aminotransferase, aldolase, total acid phosphatase, isocitrate hydrogenase, magnesium and phosphate. Columns 6-8 teach how the presence of hemoglobin is detected with column 8 lines, 10-36 being particularly relevant to the instant claims. This section of column 8 teaches the use

of a reflectance meter, the use of a direct measurement (no chromogenic reagent is used) and forming a calibration graph to determine the concentration of hemoglobin present. Columns 8-9 teach how the measurement of the hemoglobin concentration is used to correct the analyte measurement. Of particular interest is column 9, lines 44-56 teaching the relationships between hemolyzed red blood cells, the concentration of Hb, and the elevation of blood analytes such as potassium ion concentration. The relationship for potassium is taught as a linearly dependent relationship. As a result, those of ordinary skill in the art will be able to pre-select a value of hemolysis which corresponds to both a known concentration of Hb in plasma and the corresponding color thereof, which in turn correlates to a pre-selected elevation in the potassium ion concentration.

In the patent Sagusa teaches a colorimetric method for samples including interfering chromogens from the presence of chyle, hemolysis and icterus. Column 3 discusses how these things interfere with the analysis of the analytes. Color former is added to blood serum sample color it, and measurements for specific components are determined based on the light absorbance caused by coloring. For one sample, a differential light absorbance between two wavelengths at each of long wavelength region, middle wavelength region and short wavelength region within a visible wavelength band is determined. The degree of chyle is determined from the measurements for the long wavelength region, the degree of hemolysis is determined from the measurements for the middle wavelength region, and the degree of icterus is determined from the measurements for the short wavelength region. The measurements for the specific components are then corrected by the degree of chyle, degree of hemolysis and degree of icterus to obtain highly correct measurements. Column 4 shows some example wavelengths and columns 4-5 show how the degree of chyle, hemolysis and icterus are obtained and used to correct the analyte concentration. In this discussion equation (4) is particularly important because it shows that the relationship between each of the degree of chyle, hemolysis and icterus and the respective analytes are linear depending only on a constant and the concentration representative of the degree of chyle, hemolysis and icterus.

In the abstract Christenson discusses hemoglobin based blood substitutes and their interference with routine chemical tests.

In the abstract Leissing discusses modification of clinical chemistry methods to overcome interferences from diaspirin crosslinked hemoglobin (DCLHb).

In the paper Mullins discusses effects of Fluosol-DA (artificial blood) on clinical chemistry tests and instruments. Artificial blood must be added to the list of therapeutic agents that produce interference with diagnostic laboratory tests. Fluosol-DA (Alpha Therapeutic Corp., Los Angeles, CA), a stable 20% emulsion of perfluorocarbons in aqueous medium, is being evaluated in clinical trials as a blood substitute in the United States. They investigated its effects in blood and serum samples on test results and instruments in the clinical chemistry laboratory. The 20% emulsion was added to blood or serum specimens in amounts corresponding to the replacement of in-vivo plasma volumes of 10-50%, concentrations that would be expected in blood samples obtained from patients who have received Fluosol. Observed interferences mimicked those caused by high triglyceride concentrations in serum specimens: interference with chemical reactions and generation of spurious absorbance readings because of turbidity. These types of errors are often additive, and the cumulative effect may cause either erroneously high or low values for the analytes concerned. Because Fluosol may be used widely, although infrequently, for patients refusing blood transfusions on religious grounds and for patients with rare antibodies to red blood cells who require transfusion, laboratories analyzing specimens containing Fluosol should be aware of the potential errors.

In the paper Simon discusses a "pseudo-hemolytic" transfusion reaction caused by intravenous iron-dextran therapy. Intravenous iron-dextran therapy can cause a red-brown discoloration of the plasma, simulating a hemolytic transfusion reaction. A rapid and simple test to differentiate between true hemolysis and plasma discoloration due to circulating iron-dextran complexes is described.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include substances such as blood substitutes recognized by Christenson, Leissing, Mullins or Simon as interfering substances and other known interfering substances such as those taught by Sagusa or Davis into the interference correction methods of DeGrella, Corns or Waymack because of the recognized possibility for interference with clinical chemistry tests and the projected use of these substances in humans as taught by Christenson, Leissing, Mullins or Simon. It would have been obvious to one of ordinary skill in the art at the time the invention

was made to determine the effect of the interfering substance on the measurement result as taught by Davis in the DeGrella, Corns or Waymack methods and develop a calibration equation for each interfering substance because as shown by Davis an interfering substance such as hemoglobin from hemolysis can affect the measured concentration of the analyte even though its color may not directly interfere at the measurement wavelength.

6. Applicant's arguments filed June 6, 2005 have been fully considered but they are not persuasive. Applicant's argument relative to the two measurements being carried out of different instruments are not supported by the specification as originally filed. Because applicant amended the claims and presented this argument the new matter and clarity rejections have been added. Because of these problems, the argument is not commensurate in scope with the claims and the claims have been treated as including the analyzer and spectrophotometer being the same instrument. In previous searching, to determine what art might be available, examiner realized that the sample or serum blank of the DeGrella, Corns or Waymack references is equivalent to the measurement of subparagraph ii) in claims 8 and 38. As is clearly shown in these references this sample or serum blank is being used to correct for interfering substances in the analyses presented. The Davis reference clearly deals with correction of analyses in the presence of an interfering substance such as hemoglobin from hemolysis of a blood sample and it separates the detection of the interfering substance from the detection of the analyte. Davis also clearly teaches the detection of the hemoglobin from hemolysis in the absence of a chromogenic reagent (column 8, lines 18-36). Relative to claim 8, the relationship in Davis between the hemoglobin concentration and the potassium concentration is linear. This same relationship exists in Sagusa between each of the interfering substances and the analyte being measured. Thus the use of a linear relationship would have been expected for the relationship with at least the interfering substances taught by Sagusa particularly in view of the fact that hemoglobin, the interfering substance of Davis, is one of the interfering substances taught in Sagusa. Sagusa also clearly shows that one of skill in the art would have recognized that other things interfere with the analysis of components of blood and therefore would have motivated one of skill in the art to include other potential interfering materials into the correction process. This is also shown in the Corns reference. The Davis reference recognizes that the presence of an interfering substance can affect the results (interfere) in two ways: increasing the concentration of a measured

component from is release from the red blood cells through hemolysis and through interfering with the color formed in the analysis. The Sagusa reference shows that one of skill in the art also recognizes that interferences can interfere by overlapping the spectrum used to measure the analyte (the second method taught by Davis). Thus when the Christenson, Leissing or Mullins references teach that blood substitutes also interfere with the analysis of analytes, it would have been obvious to include them into the process for correcting the concentration of known interfering substances to overcome the known affects of an interfering compound. The presence of substances in the blood (blood substitutes) that would also interfere with an analysis in a manner similar to hemolysis is shown by the secondary references as well as means to remove the influence of the interfering compounds. Thus it would have been obvious to modify the teachings of DeGrella, Corns or Waymack to include the possibility of pseudohemolysis due to its recognized presence and effects on the analysis of other components of a blood sample. Since the references are dealing with interfering substances in an analysis they are properly combinable. The Courts have recognized that a secondary reference does not need to be physically combinable with the primary reference to render the invention under review obvious. Along these lines applicant is directed to *In re* Sneed 218 USPQ 385, 389 (Fed. Cir. 1983) and *In re* Keller 208 USPQ 871, 880 (CCPA 1981) .

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to correction of interferences and the use of a

sample or serum blank in correcting analytical results. Several of these reference are equivalent to the applied DeGrella, Corns or Waymack references. Of not is the Hubsch reference teaching that the work presented in the paper demonstrates the necessity of using a sample blank.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner's schedule is variable between the hours of about 6:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Arlen Soderquist
Primary Examiner